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'If at first you don't succeed, try again'. Looking beyond the initial results of a failed tuberculosis diagnosis

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We report the outcome of investigations conducted in 73 human immunodeficiency virus (HIV) infected Ugandan adults presumed to have pulmonary tuberculosis (PTB). Following initial investigations, 32 of 73 patients were diagnosed with PTB. Of the remaining 41 patients initially classified as 'non-PTB', six had a delayed PTB diagnosis after a median of 6 weeks. Of the six patients lost to follow-up, four (66%) were reported to have died. Active tracking and close monitoring of HIV-infected patients presumed to have PTB independently of initial investigation results may reduce morbidity and mortality among this vulnerable patient group.

Uganda is among the world's 22 high tuberculosis (TB) burden countries, with the World Health Organization (WHO) reporting 47 650 new cases in 2013, of which 48% were human immunodeficiency virus (HIV) co-infected.¹ The primary prevention measure is timely TB diagnosis, which remains challenging.² In immunosuppressed patients with TB, atypical clinical or radiological features, false-negative sputum microscopy findings are common,³ resulting in missed or delayed diagnosis. This is associated with increased mortality, and may contribute to ongoing TB transmission. The WHO therefore recommends intensive case finding (ICF), particularly in HIV-infected individuals.⁴ ICF consists of screening for symptoms of active TB at every encounter with a health care facility. A patient is considered a presumptive TB patient if he/she reports any of the following symptoms: current cough, fever, weight loss or night sweats. Presumed TB patients need to undergo further investigations in accordance with national guidelines and depending on the availability of diagnostic procedures.

METHODS

Uganda's Infectious Diseases Institute (IDI) cares for approximately 8000 HIV-infected individuals in Kampala. Since 2008, patients have been investigated for TB by trained staff supervised by a senior medical officer in an integrated TB-HIV clinic.⁵ Approximately 450 presumed TB patients are seen annually, of which 300 are diagnosed with TB.

We assessed clinical outcomes among HIV-infected presumed pulmonary TB (PTB) patients identified using ICF and screened for a clinical trial, who were classified as having 'no PTB' after initial investigations performed between 29 April and 9 July 2013.

In accordance with the trial's inclusion criteria, patients aged >18 years presumed to have a first episode of PTB were selected. As recommended by the WHO, investigations included chest X-ray, two sputum smear tests and an Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) result if the sputum smear results were negative or unavailable.⁶ *Mycobacterium tuberculosis* culture (Löwenstein-Jensen incubated at 37°C for 8 weeks and MGIT™ [Mycobacteria Growth Indicator Tube; BD, Sparks, MD, USA] incubated at 37°C for 6 weeks) was ordered for every patient. Data were retrospectively collected from patient files and electronic medical records from initial presentation up to October 2014. Patients lost to follow-up, defined as failure to return to the clinic for 3 consecutive months, were also contacted by telephone.

The study was reviewed and approved by the Makerere University Faculty of Medicine Research and Ethics Committee, Kampala (approval number: 120-2009), and the Uganda National Council for Science and Technology, Kampala, Uganda (HS 683).

RESULTS

During the study period, 73 HIV-infected adults were investigated for PTB. Outcomes of investigations are shown in the Figure. Following initial investigations, 32/73 (43.8%) were diagnosed with PTB based on positive sputum smear, culture or Xpert results. The remaining 41 patients were classified as having 'no PTB' on the basis of clinical, radiological and mycobacterial findings. Of the 41 patients, 36 (87.8%) were smear- and culture-negative; 5 (12.2%) were unable to produce enough sputum, and therefore only had negative results on Xpert. As shown in the Table, the demographic characteristics of patients diagnosed with PTB and patients classified as having 'no PTB' were similar, apart from a lower median CD4 cell count among patients diagnosed with PTB. Patients classified as having no PTB were treated with antibiotics for presumed lower respiratory tract infection. The majority of these patients (29/41, 70.1%) experienced complete resolution of symptoms.

Due to lack of clinical improvement after antibiotic treatment, 6/41 (14.6%) patients were re-assessed and underwent further investigations. All 6 patients were diagnosed with TB within 3 months (mean duration 6 weeks), accounting for a total of 38 TB diagnoses, 15.8% (6/38) of which were delayed. For one patient, the delay was due to delayed

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KEY WORDS

intensive case finding; HIV; TB investigations; active follow-up

AVB and CS contributed equally to this work; JF and BC contributed equally to this work.

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TABLE Clinical and demographic characteristics of patients diagnosed with PTB and those classified as having 'no PTB' after initial investigations

Characteristics	PTB* (n = 32) n (%)	'No PTB'* (n = 41) n (%)	P value†
Age, years, median [IQR]	34.5 [26–43]	36 [32–41.5]	0.301
Male sex	17 (53.1)	13 (31.7)	0.065
CD4 cell count, cells/ μ l, median [IQR]	69 [9–385]	312 [224–435]	0.02
BMI, kg/m ² , median [IQR]	19.0 [16.5–22.4]	20.9 [17.8–22.9]	0.18
On antiretroviral treatment	12 (37.5)	20 (48.8)	0.335
Symptoms			
Cough	32 (100)	41 (100)	—
Fever	26 (81.2)	26 (63.4)	0.095
Night sweats	25 (78.1)	23 (56.1)	0.049
Weight loss	28 (87.5)	19 (46.3)	0.000

*Diagnosis after initial investigations.

†Wilcoxon rank-sum test.

PTB = pulmonary tuberculosis; IQR = interquartile range; BMI = body mass index.

sputum culture, as his time to positivity was 28 days but the laboratory returned the final result only after more than 8 weeks. One patient was diagnosed using repeat Xpert, and four patients were diagnosed with disseminated TB using repeat chest X-ray, abdominal ultrasound and lymph node biopsy. By the time they were diagnosed with TB, three (50%) had been started on antiretroviral treatment (ART) based on immunological criteria.

The remaining 6 patients (6/41, 14.6%) were lost to follow-up: 2/6 (33%) were not reachable by phone, while the remaining 4/6 (66%) were reported by their relatives to have died.

DISCUSSION AND CONCLUSIONS

Delayed TB diagnosis is a commonly encountered problem globally.⁷ Delayed diagnosis attributed to health care factors includes mistaking an atypical clinical presentation for a bacterial, fungal or parasitic infection in patients with smear-negative TB.⁸ A cross-sectional study conducted in two districts

outside of Kampala in 2014 found that 88% of patients treated for PTB experienced a health care-related treatment delay.⁹

Although additional diagnostic procedures were available in this clinical trial setting, TB diagnoses were delayed in 6/38 (15.8%) TB cases. Continued clinical monitoring and enhanced diagnostics led to an accurate diagnosis. As symptoms were persistent and not newly occurring, new TB was not suspected after the initial investigation. Immune reconstitution inflammatory syndrome following initiation of ART in 3/6 patients with delayed TB diagnosis most likely contributed to case finding, a phenomenon known as 'unmasking TB'.

The majority (4/6, 66%) of the patients lost to follow-up were reported to have died, while the remaining two were not traceable. This finding emphasises the importance of active tracing and close follow-up of patients investigated for TB. This observation has led the integrated TB-HIV clinic at the IDI to adopt new internal standard operating procedures: all presumed TB cases classified as 'no TB' after investigations will be followed up at least every 2 weeks and actively traced through phone calls and home visits if they do not return for their appointments. We believe these measures will contribute to reducing morbidity and mortality among our patients, and increase the number of TB diagnoses.

Our study findings are limited by the small sample size. Nevertheless, these data reflect our day-to-day clinical experience and sparked a review of standard operating procedures. Our findings suggest that 'excluding TB' is not a one point in time decision but rather a complex diagnostic process. Future studies should address whether the additional costs of further investigations warrant diagnostic gains.

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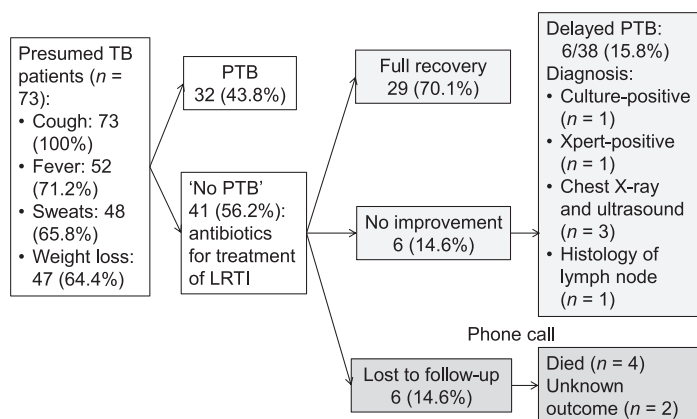


FIGURE Outcome of investigations among human immunodeficiency virus infected patients presumed to have TB at the Infectious Diseases Institute in Kampala, Uganda, 29 April–9 July 2013. TB = tuberculosis; PTB = pulmonary TB; LRTI = lower respiratory tract infection.

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Nous rapportons le résultat d'investigations réalisées chez 73 adultes Ougandais positifs au virus de l'immunodéficience humaine (VIH) et présumés d'avoir une tuberculose pulmonaire (TBP). Après les investigations initiales, 32 de 73 patients ont eu un diagnostic de TBP. Sur les 41 patients restants initialement classés comme « pas de TBP », six ont eu un diagnostic de TBP retardé après un délai médian

de 6 semaines. Sur les six patients perdus de vue, quatre (66%) sont décédés. Une recherche active et un suivi rapproché des patients VIH positifs présumés d'avoir une TBP indépendamment des résultats des investigations initiales pourrait réduire la morbidité et la mortalité dans ce groupe de patients vulnérables.

En el presente artículo se comunican los resultados de las investigaciones realizadas en 73 adultos ugandeses aquejados de infección por el virus de la inmunodeficiencia humana (VIH), en quienes existía la presunción clínica de tuberculosis pulmonar (TBP). Tras los exámenes iniciales se emitió el diagnóstico de TBP en 32 de los 73 pacientes. De los 41 pacientes restantes, clasificados inicialmente 'sin TBP', este diagnóstico se estableció de manera tardía

en seis de ellos y la mediana del plazo hasta el diagnóstico fue 6 semanas. Se notificó la defunción de cuatro de los seis pacientes perdidos de vista durante el seguimiento (66%). La localización activa y el seguimiento estrecho de los pacientes con infección por el VIH y presunción clínica de TBP, sea cual fuere el resultado de las investigaciones iniciales, disminuirían la morbilidad y mortalidad en este grupo de pacientes vulnerables.